BEFORE

THE UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH
NATIONAL TOXICOLOGY PROGRAM
OFFICE OF THE REPORT ON CARCINOGENS

COMMENTS OF THE

AMERICAN HERBAL PRODUCTS ASSOCIATION

ON

Request for Information on Nominations for the Report on Carcinogens (RoC): *Ginkgo biloba*; Goldenseal; and Kava

October 18, 2013

The American Herbal Products Association (AHPA) is the national trade association and voice of the herbal products industry, comprised of companies doing business as growers, processors, manufacturers, and marketers of herbs and herbal products, including herbal supplements and other dietary supplements. AHPA serves its members by promoting the responsible commerce of products that contain herbs, including dietary supplements.

Most of AHPA's members are companies that either sell bulk herbs or herbal extracts; that manufacture or process herbal ingredients or consumer goods containing herbs, including dietary supplement and food products for humans or animals; or that market consumer goods containing herbs, including dietary supplement and food products for humans or animals. Numerous of these companies sell products that contain as ingredients various extracts of *Ginkgo biloba* leaf, various extracts of kava (*Piper methysticum*), or goldenseal (*Hydrastis canadensis*) root.

Background and subject of these comments

In a Federal Register notice dated September 20, 2013 (the September 20 notice) the National Toxicology Program (NTP) requested information on several substances that have been nominated for possible review for future editions of the Report on Carcinogens (RoC), including substances identified in the September 20 notice as "*Ginkgo biloba* extract," "Goldenseal root powder (*Hydrastis canadensis*)," and "Kava kava extract."

In the September 20 notice NTP requested certain specific information on each of these substances, including data on current production, use patterns, and human exposure; information about published, ongoing, or planned studies related to evaluating carcinogenicity; scientific issues important for assessing carcinogenicity of the substance; and names of scientists with expertise or knowledge about the substance.

The present comments provide information in one or more of these areas for herbal ingredients consisting of or derived from *Ginkgo biloba* leaf, goldenseal (*Hydrastis canadensis*) root, and kava (*Piper methysticum*) root.

***Ginkgo biloba* leaf**

Scientific issues important for assessing carcinogenicity.

- *There is not a single substance that can be identified as "Ginkgo biloba extract."*

  The specific substance derived from the *Ginkgo biloba* plant nominated to the RoC is identified in the September 20 notice as "*Ginkgo biloba* extract."

A basic tenet of the manufacture of herbal extracts, however, is that the exact identity of an extract prepared from any herbal species is dependent on numerous factors, including, for example, the milling method, cut size, extraction solvent, extraction method, extraction temperature and time, ratio of solvent to biomass, purification methods, excipients, drying methods, and targeted levels in the finished extract of any of naturally-occurring constituents or contaminants present in the source herbal material.

There can therefore be many different and unique extracts of a single herb, each of which must be recognized to be a separate substance for purposes of evaluation of safety. This is true even when the source herb itself presents toxicity concerns, and an extract that completely removes any constituent known to be the basis of such toxicity should be evaluated differently than another extract that does not.

At the same time, companies may set and control for specifications for the manufacture of an herbal extract in a manner that assures that each lot of an extract manufactured by that company is consistent from batch-to-batch. But it would be scientifically unsound to assume that any such manufacturer-specific consistency in any way implies or otherwise indicates that one company's well-controlled extract is the same ingredient as an extract manufactured from the same source herb by another company, using entirely different processes and to different specifications.

In other words, and as relevant to the specific nomination identified here, there are many different and unique substances that can be described as "*Ginkgo biloba* [leaf] extract." For example, at least two CAS numbers have been registered for extracts of *Ginkgo biloba* leaf, one of which (90045-36-6) has a rather general description while the other (122933-57-7) is quite specific to a particular brand identified as EGb 761, a proprietary extract manufactured by Dr. Willmar Schwabe GmbH & Co. Each separate finished extract of *Ginkgo biloba* leaf may have numerous similarities to other *Ginkgo biloba* leaf extracts, and importantly, may also have significant differences. In order to evaluate any one of these extracts for the RoC, the specific identity of the extract under consideration must be established.

- *Evidence of toxicity of one specific extract of an herb cannot be extrapolated to another extract of the same herb*.

  Concerns about the safety, including evidence of carcinogenic activity, of one extract of a source herb cannot be automatically transferred to any other extract of the same herb. This is because, as discussed above, there are many different and unique substances that can be manufactured through variations in extraction processes that start with a single herbal source ingredient.

Recognizing this scientific fact, the U.S. Senate Committee on Appropriations recorded the following statement in its Report to accompany appropriations for the fiscal year ending September 30, 2014 for Departments of Labor, Health and Human Services, and Education:

> *National Toxicology Program [NTP].-*The Committee urges NTP to be highly precise when describing the results of its studies on particular extracts of an herbal species to avoid any possible confusion about the relevance of such studies to other extracts of the species.

As an example, comfrey (*Symphytum officinale*) root is known to contain pyrrolizidine alkaloids (PAs), which are in turn known to have mutagenic properties. But there are in the marketplace comfrey root extracts that have been manufactured with an extraction process that removes the PAs. A study conducted on one such PA-free comfrey root extract showed that this specific extract was "not mutagenic in the bacterial reverse mutation assay."[1] Any extrapolation of safety concerns about whole comfrey root to this extract is therefore scientifically unsound and in fact inaccurate.

Any such extrapolation of research on one extract of an herbal ingredient in which the specific compound responsible for a known or observed toxicity has not been identified to another unique extract of that same herb is also scientifically unsound.

- *The specific* Ginkgo biloba *leaf extract studied by NTP is a unique and patented ingredient.*

  NTP conducted 2-year gavage studies on one specific brand of a *Ginkgo biloba* leaf extract, manufactured by Shanghai Xing Ling Scientific & Technology Pharmaceutical Co. Ltd. (Shanghai Xing Ling) and branded by that company as GBE-50. The results of this study were presented in NTP Technical Report 578 (NTP TR 578), dated March 2013.

  NTP TR 578 clearly states that the tested *Ginkgo biloba* leaf extract was supplied by Shanghai Xing Ling and provides data to characterize the ingredient, but does not specifically state that the ingredient was the GBE-50 brand. In a letter dated October 10, 2001 to NTP, however, Shanghai Xing Ling identifies the material to be its GBE-50 branded product and provides the following information to describe it:

  > "We are so pleased that your program be interested in our Ginkgo biloba extract-50 (GBE-50), which the technology patented in U.S. (U.S. Patent No. 6,030,621),

[1] Benedek B, A Ziegler and P Ottersbach. March 2010. Absence of mutagenic effects of a particular Symphytum officinale L. liquid extract in the bacterial reverse mutation assay. *Phytother Res* 24(3):466-468.

and is applying to get approve by U.S. FDA for clinical trial as IND. It is a type II new drug in China, which approved by the State Drug Administration of China.

"The GBE-50 contains over 44% total ginkgo flavonoids (in which over 24% are ginkgo flavonol glycosides); and total ginkgo lactones over 6%. It controls ginkgolic acid less than 5 PPM."

Shanghai Xing Ling has actually obtained at least four U.S. patents for its GBE-50 brand *Ginkgo biloba* leaf extract.[2] This extract has been described "as a new multicomponent drug" in the scientific literature.[3, 4] It is clear from reviewing the company's patents that Shanghai Xing Ling has intentionally developed a unique *Ginkgo biloba* leaf extract that is intended to be dissimilar to other ginkgo leaf extracts. The patent referred to in the above cited letter to NTP (i.e., U.S. Patent No. 6,030,621) includes several statements that clearly establish the GBE-50 brand as dissimilar to other *Ginkgo biloba* leaf extracts sold in the U.S. For example, this patent (*emphasis added* throughout):

- States that one object of the company's invention of this specific and proprietary ginkgo leaf extract is "to provide a Ginkgo biloba extract with a ***highly concentrated effective content***, that include 44 to 78% flavonoids, 2.5 to 10% ginkgolides and 2.5 to 10% bilobalide."
- States, "***Until now it has not been possible*** to prepare such highly concentrated extracts from Ginkgo biloba leaves."
- Identifies an "advantage of a Ginkgo biloba extract with highly concentrated effective content" as "the ***reduced daily dosage*** and smaller size of the pharmaceutical prepared from it."
- Claims another "advantage of a Ginkgo biloba extract with highly concentrated effective content" to be "***further removal of inactive substances***," apparently meaning removal of any constituents other than the flavonoids or terpene lactones.
- Notes that the patent "relates generally to compositions extracted from Ginkgo biloba leaves and particularly to a ***different composition comprising new active components and combinations***."

[2] U.S. Patents 06030621, 06187314, 06475534, and 06632460.

[3] Liu A, Zhang Z. [Effect of GBE50 on action potentials in normal and simulated ischemic guinea pig papillary muscles]. *Zhongguo Zhong Yao Za Zhi*. 2010 Sep;35(17):2342-5. [Article in Chinese].

[4] Liu AH, Zhang ZX, Wang XY. [Effect of GBE50 on delayed rectifier potassium current of ventricular myocytes in ischemic guinea pig]. *Zhongguo Ying Yong Sheng Li Xue Za Zhi*. 2010 Nov;26(4):444-8. [Article in Chinese].

> In summary, Shanghai Xing Ling's GBE-50 brand is clearly a different, unique, and proprietary *Ginkgo biloba* leaf extract. The ginkgo leaf extract described in its U.S. patents is novel and "until now … has not been possible" to produce; contains "more highly concentrated" levels of flavonol glycosides than other such extracts; seeks "further removal" of any other constituents naturally found in ginkgo leaf; is of a "different composition" than other ginkgo leaf extracts; and allows for a "reduced daily dosage."
>
> It would therefore be scientifically unsound to extrapolate the results reported in NTP TR 578 to any other *Ginkgo biloba* leaf extract.

Knowledgeable scientists. AHPA has identified Dr. Egon Koch as a scientist with significant expertise and knowledge about *Ginkgo biloba*. Dr. Koch is Head of Preclinical Research, Dr. Willmar Schwabe GmbH & Co. KG, 76227 Karlsruhe, Germany. His *curriculum vitae* is appended to these comments; he can be contacted at egon.koch@schwabe.de.

Data on current production, use patterns, and human exposure. AHPA does not have any quantitative information on production, use patterns, or human exposure for *Ginkgo biloba* leaf extracts generally.

AHPA does, however, have some information on the use patterns of the GBE-50 brand *Ginkgo biloba* leaf extract manufactured by Shanghai Xing Ling and the subject of NTP's study as recorded in NTP TR 578. Although NTP TR 578 reports that this proprietary ingredient was "widely distributed in commerce," presumably meaning in the United States, and presumable related to human oral consumption, this statement is inaccurate.

This statement of wide distribution of this ingredient was attributed to a personal communication from Po Chan, Ph.D., one of the authors of NTP TR 578. But in an October 16, 2001 email to other NTP staff (John Bucher and Cynthia Smith) obtained by AHPA through requests submitted under the Freedom of Information Act, Dr. Chan communicated that he was introduced to the supplier of the ingredient used by NTP in its study by a "contact at Proctor & Gamble" who informed him that this supplier "is a major producer of ginkgo and is shipping the product to many so called distributors and manufacturers in Europe and the U.S. including Proctor & Gamble."

AHPA has consulted with Proctor & Gamble, however, and been informed that the only ginkgo-containing product that the company ever sold was a lotion in the Olay® product

line, and that it has not marketed any oral-dosage products with any *Ginkgo biloba* leaf ingredient.

In addition, AHPA contacted Shanghai Xing Ling through a Chinese speaking representative of one AHPA member, who was informed that Shanghai Xing Ling does not sell or market any of its own products that contain GBE-50 in the United States. In addition, AHPA has never encountered the GBE-50 ingredient in the U.S. market and is not aware of any ingredient supplier who offers for sale any *Ginkgo biloba* leaf extract that is standardized to contain more than 24% flavonol glycosides and 6% terpene lactones.

Any consideration to NTP TR 578 must therefore be mitigated by the fact that there is no information to support the assertion that the tested *Ginkgo biloba* leaf extract, Shanghai Xing Ling's GBE-50, has ever been included in any product marketed in the U.S. for oral use. The report from Dr. Chan's Proctor & Gamble contact that Shanghai Xing Ling was a "major producer of ginkgo" should be dismissed as hearsay, at least as far as the U.S. marketplace is concerned.

In addition, AHPA understands that the most commonly sold *Ginkgo biloba* leaf extract worldwide is the EGb 761 brand manufactured by Dr. Willmar Schwabe GmbH. The company has provided AHPA with the following relevant data on use patterns and human exposure to this specific ingredient:

- Between 1989 and 2012 approximately 8.709 million oral defined daily doses of the standardized Ginkgo biloba leaf extract EGb 761® were placed on the international market worldwide.
- The standard daily oral dose of EGb 761 is 120 mg.

<u>Studies evaluating carcinogenicity of any specific *Ginkgo biloba* leaf extract.</u> AHPA is aware of just one study that evaluated the carcinogenicity of the GBE-50 brand of *Ginkgo biloba* leaf extract manufactured by Shanghai Xing Ling Scientific & Technology Pharmaceutical Co. Ltd. This is the study undertaken by NTP as recorded in NTP Technical Report 578 (March 2013).

AHPA is also aware of the following studies that have been conducted on the EGb 761 brand of *Ginkgo biloba* leaf extract manufactured by Dr. Willmar Schwabe GmbH, each of which will be provided upon request:

Genotoxicity studies performed with EGb 761®

- Neumann W. (1984). Mutagenicity Study of PSc 44 in the Ames Salmonella / Microsome Plate Test (in vitro); LPT Report.

- Allen J. A. (1989). An Assessment of the Mutagenic Potential of J-121 Using the Mouse Lymphoma TK Locus Assay; Huntingdon Report No. HYW5/881803.
- Brooker, P. C. (1988). J-121: Metaphase Chromosome Analysis of Human Lymphocytes Cultured in Vitro; Huntingdon Report No. HYW3/88866.
- Henderson I. M. (1988). Mouse Micronucleus Test on J-121; Huntingdon Report No. HYW2/88417.
- Kitching J. (1999). EGb 761: Bacterial Mutation Assay; Huntingdon Report No. SHB046/993358.
- Leuschner J (2008). Micronucleus Test of EGb 761 in Bone Marrow Cells of the Mouse by Oral Administration. LPT Report No. 22993.
- Leuschner J. (2009). Mutagenicity study of Ginkgo biloba extract 501282080/Ex. Ch. 249 in Mammalian Cells (V79) in the in Vitro Gene Mutation Assay (HPRT Test). LPT Report No. 21783.
- Leuschner J (2013). Micronucleus Test of Ginkgo biloba extract EGb 761 and Ginkgo biloba extract NTP in Bone Marrow Cells of the NMRI Mouse Following Oral Administration. LPT Report No. 29879.

Carcinogenicity studies performed with EGb 761®

- Gazeley, M. J. S. (1994). Ginkgo Extract EGb 761 (RH 44): Oral (Dietary Administration) Carcinogenicity Study in the Mouse; Hazleton Report No. 7488-690/10.
- Hill, R. E. (1989). RH 44: 52 Week Dietary Toxicity Study in the Rat. Toxicol. Lab. Report No. RHC/2/89.
- Statement on a Possible Genotoxic and Carcinogenic Potential of the Ginkgo biloba leaf Extract EGb 761®.

Kava (*Piper methysticum*) root

Scientific issues important for assessing carcinogenicity.

- *There is not a single substance that can be identified as "kava extract."*

  The specific substance derived from the *Piper methysticum* plant nominated to the RoC is identified in the September 20 notice as "kava kava extract," referred to hereinafter as "kava extract" or "kava root extract."

  A basic tenet of the manufacture of herbal extracts, however, is that the exact identity of an extract prepared from any herbal species is dependent on numerous factors, including, for example, the milling method, cut size, extraction solvent, extraction method, extraction temperature and time, ratio of solvent to biomass, purification methods, excipients, drying methods, and targeted levels in the finished

extract of any of naturally-occurring constituents or contaminants present in the source herbal material.

There can therefore be many different and unique extracts of a single herb, each of which must be recognized to be a separate substance for purposes of evaluation of safety. This is true even when the source herb itself presents toxicity concerns, and an extract that completely removes any constituent known to be the basis of such toxicity should be evaluated differently than another extract that does not.

At the same time, companies may set and control for specifications for the manufacture of an herbal extract in a manner that assures that each lot of an extract manufactured by that company is consistent from batch-to-batch. But it would be scientifically unsound to assume that any such manufacturer-specific consistency in any way implies or otherwise indicates that one company's well-controlled extract is the same ingredient as an extract manufactured from the same source herb by another company, using entirely different processes and to different specifications.

In other words, and as relevant to the specific nomination identified here, there are many different and unique substances that can be described as "Kava [root] extract." Each separate finished extract of *Piper methysticum* root may have numerous similarities to other *Piper methysticum* root extracts, and importantly, may also have significant differences. In order to evaluate any one of these extracts for the RoC the specific identity of the extract under consideration must be established.

An additional factor as relates to kava is that throughout the South Pacific where kava is commonly consumed there are approximately 150 different cultivars, distributed to eight chemotypes with a stable composition and distribution with respect to the phytochemical class of kavalactones. Traditional use has always favored kava cultivars with a high relative quantity of kavalactone, whereas minor kavalactone constituents, such as methysticin or yangonin, are never predominant. There is a local differentiation in good = "noble" kava, suitable for daily consumption, and the so called "two day" cultivars known to produce hang-over and adverse effects and therefore avoided for daily consumption. Any evaluation of the carcinogenicity of any individual extract of kava must take into account the specific cultivar used.

- *Evidence of toxicity of one specific extract of an herb cannot be extrapolated to another extract of the same herb*.

  Concerns about the safety, including evidence of carcinogenic activity, of one extract of a source herb cannot be automatically transferred to any other extract of the same herb. This is because, as discussed above, there are many different and unique

substances that can be manufactured through variations in extraction processes that start with a single herbal source ingredient.

Recognizing this scientific fact, the U.S. Senate Committee on Appropriations recorded the following statement in its Report to accompany appropriations for the fiscal year ending September 30, 2014 for Departments of Labor, Health and Human Services, and Education:

> *National Toxicology Program [NTP].*-The Committee urges NTP to be highly precise when describing the results of its studies on particular extracts of an herbal species to avoid any possible confusion about the relevance of such studies to other extracts of the species.

As an example, comfrey (*Symphytum officinale*) root is known to contain pyrrolizidine alkaloids (PAs), which are in turn known to have mutagenic properties. But there are in the marketplace comfrey root extracts that have been manufactured with an extraction process that removes the PAs. A study conducted on one such PA-free comfrey root extract showed that this specific extract was "not mutagenic in the bacterial reverse mutation assay."[5] Any extrapolation of safety concerns about whole comfrey root to this extract is therefore scientifically unsound and in fact inaccurate.

Any such extrapolation of research on one extract of an herbal ingredient in which the specific compound responsible for a known or observed toxicity has not been identified to another unique extract of that same herb is also scientifically unsound.

Knowledgeable scientists. AHPA has identified Mathias Schmidt, Ph.D., HERBresearch Germany, as a scientist with significant expertise and knowledge about *Piper methysticum*. Dr. Schmidt's *curriculum vitae* is appended to these comments; he can be contacted at schmidt@herbresearch.de.

Studies evaluating carcinogenicity of *Piper methysticum* root. AHPA is aware of numerous studies on kava that provide evidence that this herb has potential benefit as a chemopreventive and in cancer prevention and treatment. AHPA is also aware of one study on two specific extracts of kava root, apparently including the same brand as was tested by NTP, which found a lack of mutagenic response in the mouse lymphoma mutation assay. The published articles on these numerous studies follow.

Cancer chemopreventive potential:

[5] Benedek B, A Ziegler and P Ottersbach. March 2010. Absence of mutagenic effects of a particular Symphytum officinale L. liquid extract in the bacterial reverse mutation assay. *Phytother Res* 24(3):466-468.

- Steiner GG (2000). The correlation between cancer incidence and kava consumption. *Hawaii Med J* 59(11): 420-422
- Hashimoto T, Suganuma M, Fujiki H, Yamada M, Kohno T and Asakawa Y (2003). Isolation and synthesis of TNF-alpha release inhibitors from Fijian kawa (Piper methysticum). *Phytomedicine* 10(4): 309-317.
- Agarwal R and Deep G (2008). Kava, a tonic for relieving the irrational development of natural preventive agents. *Cancer Prev Res (Phila)* 1(6): 409-412.
- Johnson TE, Kassie F, O'Sullivan MG, Negia M, Hanson TE, Upadhyaya P, Ruvolo PP, Hecht SS and Xing C (2008). Chemopreventive effect of kava on 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone plus benzo[a]pyrene-induced lung tumorigenesis in A/J mice. *Cancer Prev Res (Phila)* 1(6): 430-438.
- Shaik AA, Hermanson DL and Xing C (2009). Identification of methysticin as a potent and non-toxic NF-kappaB inhibitor from kava, potentially responsible for kava's chemopreventive activity. *Bioorg Med Chem Lett* 19(19): 5732-5736.
- Johnson TE, Hermanson D, Wang L, Kassie F, Upadhyaya P, O'Sullivan MG, Hecht SS, Lu J and Xing C (2011). Lung tumorigenesis suppressing effects of a commercial kava extract and its selected compounds in A/J mice. *Am J Chin Med* 39(4): 727-742.
- Triolet J, Shaik AA, Gallaher DD, O'Sullivan MG and Xing C (2012). Reduction in colon cancer risk by consumption of kava or kava fractions in carcinogen-treated rats. *Nutr Cancer* 64(6): 838-846.

Cancer chemopreventive and treatment potential:

- Tang Y, Simoneau AR, Xie J, Shahandeh B and Zi X (2008). Effects of the kava chalcone flavokawain A differ in bladder cancer cells with wild-type versus mutant p53. *Cancer Prev Res (Phila)* 1(6): 439-451.
- Tang Y, Li X, Liu Z, Simoneau AR, Xie J and Zi X (2010). Flavokawain B, a kava chalcone, induces apoptosis via up-regulation of death-receptor 5 and Bim expression in androgen receptor negative, hormonal refractory prostate cancer cell lines and reduces tumor growth. *Int J Cancer* 127(8): 1758-1768.
- Li X, Liu Z, Xu X, Blair CA, Sun Z, Xie J, Lilly MB and Zi X (2012). Kava Components Down-Regulate Expression of AR and AR Splice Variants and Reduce Growth in Patient-Derived Prostate Cancer Xenografts in Mice. *PloS One* 7(2): e31213.

Cancer treatment potential:

- Zhao X, Chao YL, Wan QB, Chen XM, Su P, Sun J and Tang Y (2011). Flavokawain B induces apoptosis of human oral adenoid cystic cancer ACC-2

cells via up-regulation of Bim and down-regulation of Bcl-2 expression. *Can J Physiol Pharmacol* 89(12): 875-883.

- Eskander RN, Randall LM, Sakai T, Guo Y, Hoang B and Zi X (2012). Flavokawain B, a novel, naturally occurring chalcone, exhibits robust apoptotic effects and induces G2/M arrest of a uterine leiomyosarcoma cell line. *J Obstet Gynaecol Res* 38(8): 1086-1094.
- Sakai T, Eskander RN, Guo Y, Kim KJ, Mefford J, Hopkins J, Bhatia NN, Zi X and Hoang BH (2012). Flavokawain B, a kava chalcone, induces apoptosis in synovial sarcoma cell lines. *J Orthop Res* 30(7): 1045-1050.
- Warmka JK, Solberg EL, Zeliadt NA, Srinivasan B, Charlson AT, Xing C and Wattenberg EV (2012). Inhibition of mitogen activated protein kinases increases the sensitivity of A549 lung cancer cells to the cytotoxicity induced by a kava chalcone analog. *Biochem Biophys Res Commun* 424(3): 488-492.

Lack of mutagenic response:

- Whittaker P, Clarke JJ, San RH, Betz JM, Seifried HE, de Jager LS and Dunkel VC (2008). Evaluation of commercial kava extracts and kavalactone standards for mutagenicity and toxicity using the mammalian cell gene mutation assay in L5178Y mouse lymphoma cells. *Food Chem Toxicol* 46(1): 168-174.

***Hydrastis canadensis* root**

Scientific issues important for assessing carcinogenicity. NTP conducted feeding studies with goldenseal root powder, the results of which were recorded in NTP Technical Report 562 (NTP TR 562), dated August 2010. NTP TR 562 recorded a conclusion of “clear evidence of carcinogenic activity” in male and female F344/N rats. This conclusion was drawn in the absence of any carcinomas in the female rats and a single hepatocellular carcinoma in a single male rat.

But NTP has data – which was not made available at the NTP Technical Reports Review Subcommittee (TRRS) meeting at which this conclusion of “clear evidence” was accepted – on the historical control range of hepatocellular carcinomas in male F344 rats. This data shows that a single hepatocellular carcinoma in a single male F344/N rat is within the historical range for control populations of this species. The Historical Control Tumor Incidence Summary at NTP’s Toxicology Data Management System, updated as of December 1999, provides data on 20 oral feeding studies with F344 male rats. In the course of these studies, 7 hepatocellular carcinomas were observed in a total control population of 1002 male F344 rats. The summary reports the mean incidence and standard deviation as 0.7 percent and 1.5, respectively, for hepatocellular carcinomas in these 20 studies. In four of these studies, each with control populations of

50 male F344 rats, one incident of hepatocellular carcinoma was observed in the controls, and in one other such study with a control population of 49 male F344 rats, three such incidents were observed. Thus, five of these 20 studies – i.e., 25 percent of these studies – recorded at least one incident of hepatocellular carcinoma in control male F344 rats.

Given this important historical data, a review of the conclusion of "clear evidence of carcinogenic activity" of goldenseal, as recorded in NTP TR 562, is the only sound scientific approach that can be made in considering this information for the RoC.

Data on current use patterns and human exposure. Human exposure to goldenseal root, as measured in the daily oral consumption described in the most authoritative contemporary references, is 2 grams. This is the level given in the monograph on goldenseal root prepared by the American Herbal Pharmacopoeia,[6] which cites the 1946 edition of the *National Formulary* (now incorporated into the *United States Pharmacopeia*) as its source.

AHPA notes that NTP TR 562 records daily oral consumption of goldenseal root as 3 grams. The reference for this level, however, provides no citation to support this higher level. It should be recognized as an inferior reference for this information.

An additional human exposure factor for goldenseal root is its standard duration of use. Goldenseal root is not generally used on a daily or long-term basis, but is much more likely to be used only for 1-2 weeks one or two times annually. There are no usage records that indicate that goldenseal root would be used regularly or throughout the lifetime of an individual user.

Knowledgeable scientists. AHPA has identified Kerry M. Bone, B.Sc., Director Research and Development, MediHerb, Australia, as a scientist with significant expertise and knowledge about *Hydrastis canadensis*. Mr. Bone's *curriculum vitae* is appended to these comments; he can be contacted at Kerry.Bone@integria.com.

Studies evaluating carcinogenicity of *Hydrastis canadensis* root. AHPA is aware of one study on goldenseal that suggests that this herb has potential benefit as a chemopreventive, and another that suggests that it has potential benefit in cancer treatment. A bibliography of these two studies follows.

[6] Upton R (ed.). 2001. American Herbal Pharmacopoeia and Therapeutic Compendium - *Goldenseal Root Powder: Hydrastis canadensis. Standards of Analysis, Quality Control, and Therapeutics* Soquel, CA: American Herbal Pharmacopoeia.

Chemopreventive potential of a goldenseal root extract

- Saha SK, Sikdar S, Mukherjee A, Bhadra K, Boujedaini N, Khuda-Bukhsh AR. (2013). Ethanolic extract of the Goldenseal, Hydrastis canadensis, has demonstrable chemopreventive effects on HeLa cells in vitro: Drug-DNA interaction with calf thymus DNA as target. *Environ Toxicol Pharmacol*.;36(1):202-14.

Cancer treatment potential of a goldenseal root extract

- Karmakar SR, Biswas SJ, Khuda-Bukhsh AR. (2011). Anti-carcinogenic potentials of a plant extract (Hydrastis canadensis): I. Evidence from in vivo studies in mice (Mus musculus). *Asian Pac J Cancer Prev*;11(2):545-51.

AHPA appreciates the opportunity to provide these comments. Please feel free to contact me if additional information or clarification is needed.

Respectfully submitted,

[Redacted]

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